

## REMARKS

This is being filed in response to the comments in the Advisory Action dated June 9, 2004 with a Request for Continued Examination. Claims 1 to 8, 14 to 17, and 24 are pending in the application. Applicants acknowledge, with appreciation, that the Examiner has entered the amendment filed on May 17, 2004, and is considering the references filed in a supplemental Information Disclosure Statement file on May 6, 2004.

Claims 1, 2, 5-8, 14-17 and 24 have been amended to recite that the modified TNF of the invention is a “polypeptide having TNF biological activity” with polyethylene glycol covalently attached thereto. Support for the amendment may be found in the Specification at page 5, lines 23-29 wherein it is taught that the TNF proteins of the invention include TNF proteins that have been mutated without significantly impairing biological activity. Thus, no new matter is added.

Applicant respectfully requests reconsideration of the rejections of record in view of the amendments and following remarks.

### I. Rejection under 35 U.S.C. §112, second paragraph (Indefiniteness)

Claims 1 to 4, 14 to 17, and 24 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term “TNF.” Claims 1, 2, 5-8, 14-17 and 24 have been amended herein to recite that the modified TNF is a “polypeptide having TNF biological activity.” Claims 1, 14 and 16 have also been amended to include the feature that the biological activity is measured by the ability of the TNF to kill METH A tumors *in*

*vivo*. Support for the amendments may be found, for example at page 5, lines 23-29, and page 2, lines 26-28 and Examples. Thus, no new matter is added.

The Federal Circuit has stated that when “the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more.” *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986) (citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985)). One of skill in the art is reasonably apprised of the meaning of TNF and the metes and bounds of the invention are clearly set forth.

Withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

## **II. Maintained Rejections under 35 USC § 103(a) for Alleged Obviousness**

**A.** The Office Action maintains the rejection of Claims 1 to 7, 14 to 17, and 24 under 35 U.S.C. § 103(a) as allegedly obvious over Tsutsumi, Y., *et al.*, *Jpn J. Cancer Res.* 85:9-12 (1994) (“Tsutsumi I”) in view of Satake-Ishikawa, R., *et al.*, *Cell Structure and Function* 17:157-160 (1992) (“Satake-Ishikawa”) and EP 0 401 384 (“Ishikawa”).

According to the Advisory Action, the Examiner disagrees with the characterization of “Tsutsumi (*Br. J. Cancer* (1996) 74(7):1090-1095).” Specifically, the Examiner states that Tsutsumi teaches that when TNFs were the same size, those with higher molecular weight PEG molecules performed better (citing page 1091, last sentence of paragraph bridging left and right columns). However, Tsutsumi also specifically states that the object of the stdy was to “attempt to discover the optimal molecular size of PEG-TNF- $\alpha$ , which is determined by the

degree of PEGmodification and the molecular weight of the attached PEG.” (page 1093, col. 1, first paragraph under “Discussion”). As such, Tsutsumi concluded that PEG<sub>12,000</sub>-TNF- $\alpha$  Fr.3 and MPEG-TNF- $\alpha$  (PEG<sub>5,000</sub>) were the optimal molecules (See page 1094, col.2, last sentence before first full paragraph). As Tsutsumi concluded that the “optimal” molecular size PEG-modified TNF- $\alpha$  had been described in this study, there is *absolutely no motivation* to use higher molecular weight PEG. To use a higher molecular weight PEG would be to go outside of what is considered “optimal.” As with any “optimal” range, lower values and higher values would be discouraged. Thus, one of skill in the art would have no motivation to use a higher molecular weight PEG, and perhaps more importantly, would have no reasonable expectation of success that a higher molecular weight PEG (i.e., outside of the “optimal” range) would perform well.

In the hypothetical combination of reference suggested by the Office Action, Satake-Ishikawa and the Ishikawa are cited as allegedly teaching the benefits of modifying rHu-CSF with larger PEG molecules in order to achieve the desired results of improved *in vivo* activity. This is an entirely different protein than TNF- $\alpha$ . One of skill in the art would have to be motivated to try this strategy using an entirely different protein, such as TNF (as taught by the Tsutsumi I reference) which only modified TNF- $\alpha$  with PEG<sub>5,000</sub>. However, at the time the Applicants’ application was filed, one of ordinary skill in the art would have been aware that Tsutsumi had also performed the optimization of the TNF- $\alpha$  study as described above. All teachings of all art must be considered for the obviousness analysis, including those references that teach away from the hypothetical combination. In this case, Satake-Ishikawa and Ishikawa suggest using PEG with an average molecular weight of up to 20,000. This is

on *an entirely different protein* than that taught in the Tsutsumi I reference and in the Applicants' invention. Tsutsumi I and the Applicants invention involve TNF. However, Tsutsumi I teaches only a PEG with an average molecular weight of 5,000. Critically, the Tsutsumi (1996) *Br. J. Cancer* 74:1090-1095 reference teaches away from the use of higher molecular weight PEG, as it would be outside of the determined "optimal" range, and therefore, one of ordinary skill in the art would not be motivated to use high molecular weight PEG in combination with TNF with any reasonable expectation of success.

Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

**B.** The Office Action also maintains the rejection of Claims 1 and 8 under 35 U.S.C. § 103(a) as allegedly obvious over Tsutsumi I in view of Satake-Ishikawa and Ishikawa, and further in view of Mark, D.F., *et al.*, *Methods Enzymol.* 154: 403- 414 (1987) ("Mark"). As the hypothetical combination of Tsutsumi I, Satake-Ishikawa and Ishikawa fail to satisfy the legal requirements of obviousness, Mark adds nothing to make up for the fundamental deficiency in the Office Action's obviousness determination.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. U.S.C. § 103(a) over Tsutsumi I in view of Satake-Ishikawa and Ishikawa, and further in view of Mark.

**III. Rejection under 35 U.S.C. §112, first paragraph (Written Description)**

The Office Action objects to the amendment entered in the Applicants' Response filed October 14, 2003 presumably because the Examiner finds no teaching of the limitation "range of 15,000 to about 40,000" or the limitation "15,000" *in haec verba*.

Applicants respectfully invite the Examiner's attention to the MPEP 2163.06 III where range limitations are discussed. In that discussion, the MPEP notes that in *In re Wertheim*, the range disclosed in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%." A new claim limitation of "at least 35%" did not meet the Written Description Requirement as there was no upper limit (*i.e.*, it was outside the original 25%-60% upper range limit), however a limitation of "between 35% and 60%" did meet the written description requirement (note that 35% was not a specific example, but merely fell within the range of the original disclosure). This case is very similar to the situation of the present claims. It would be immediately apparent to those of skill in the art that the inventor had possession of this range at the time of filing. As noted in MPEP 2163.06 III, the Federal Circuit stated in *Union Oil of Cal. V. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232-33 (Fed. Cir. 2000) "[T]he Patent Act and this court's case law require only *sufficient* description to show one of skill in the ...art that the inventor possessed the claimed invention at the time of filing." (emphasis added).

Withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

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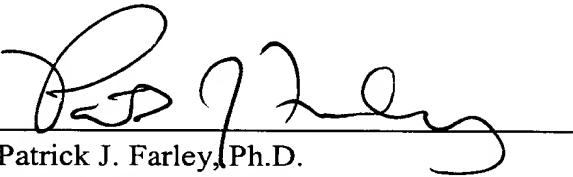
**PATENT**  
**REPLY FILED UNDER EXPEDITED**  
**PROCEDURE PURSUANT TO**  
**37 CFR § 1.116**

**IV. Conclusion**

Applicants earnestly submit that the claims are in condition for allowance.

Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,



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